Promising Directions for Improved Training, Learning, and Memory

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Abstract

The second half of the 20th century has been called the golden age of molecular biology. Many scientists believe that the first half of the 21st century may well encompass the start of a similar period for neuroscience that will leads to a deep understanding of processes in the brain. While much of today's efforts are theoretical, applications of basic science will become more common as the discipline of cognitive neuroscience matures. These advances promise to provide extremely useful insights to the training community, both military and civilian. This paper is designed as a contemporary overview of topics in cognitive neuroscience that may impact the capacity to improve training, learning, and memory for normal, unimpaired individuals engaged in a variety of tasks.

1 INTRODUCTION

Military training is a combination of instructions and applied exercises designed for the attainment and retention of knowledge, skills, and attitudes. This attainment of skills, knowledge, understanding, values, and wisdom is defined by the field of neurophysiology under the broad umbrella of "learning". All learning requires the storage and retention of information, summed up by the concept of memory. While the past decade has seen great advances in understanding better methods for training and for learning, there has also been a tremendous growth in understanding the neurological basis for learning and memory.

The incorporation of new training techniques with the latest understanding of the neural processes underpinning learning and memory is expected to lead to rapid improvement in the ability to learn, retain, and recall military training concepts and practices.

1.1 Hierarchy of Memory

Cognitive scientists have adopted the concept that memory can be divided into two categories: declarative and non-declarative. Declarative memories are described as "explicit," or those that require conscious recall. Declarative memory consists of episodic memory and semantic memory. Episodic memory refers to specific events at a particular time or place, while semantic memory refers to abstract knowledge—facts that are known but not linked to an event.

Non-declarative memories are described as being "implicit", or procedural in nature. Non-declarative memory is separated into three areas. First, skills and habits, where repetition leads to unconscious improvement in performance; second, motor-reflex learning, also known as conditioning; and finally emotional responses, including fear, anger, or helplessness.

The main difference between these two classes of memories is the neural mechanism used to store them. An indicator of this mechanism is the dependence on the hippocampus. The hippocampus is a subcortical structure of the limbic system, and is located in two places in the medial temporal lobes, one on each side of the brain. Both declarative memory modes—episodic and semantic—are dependent upon an intact hippocampus. Without a hippocampus, no new declarative memories can be stored for more than a few seconds. Damage can result in anterograde amnesia, a condition where one cannot form new memories but can continue to learn skills, develop motor reflexes, and form emotional opinions within the memories that remain. However, the amnesiac cannot

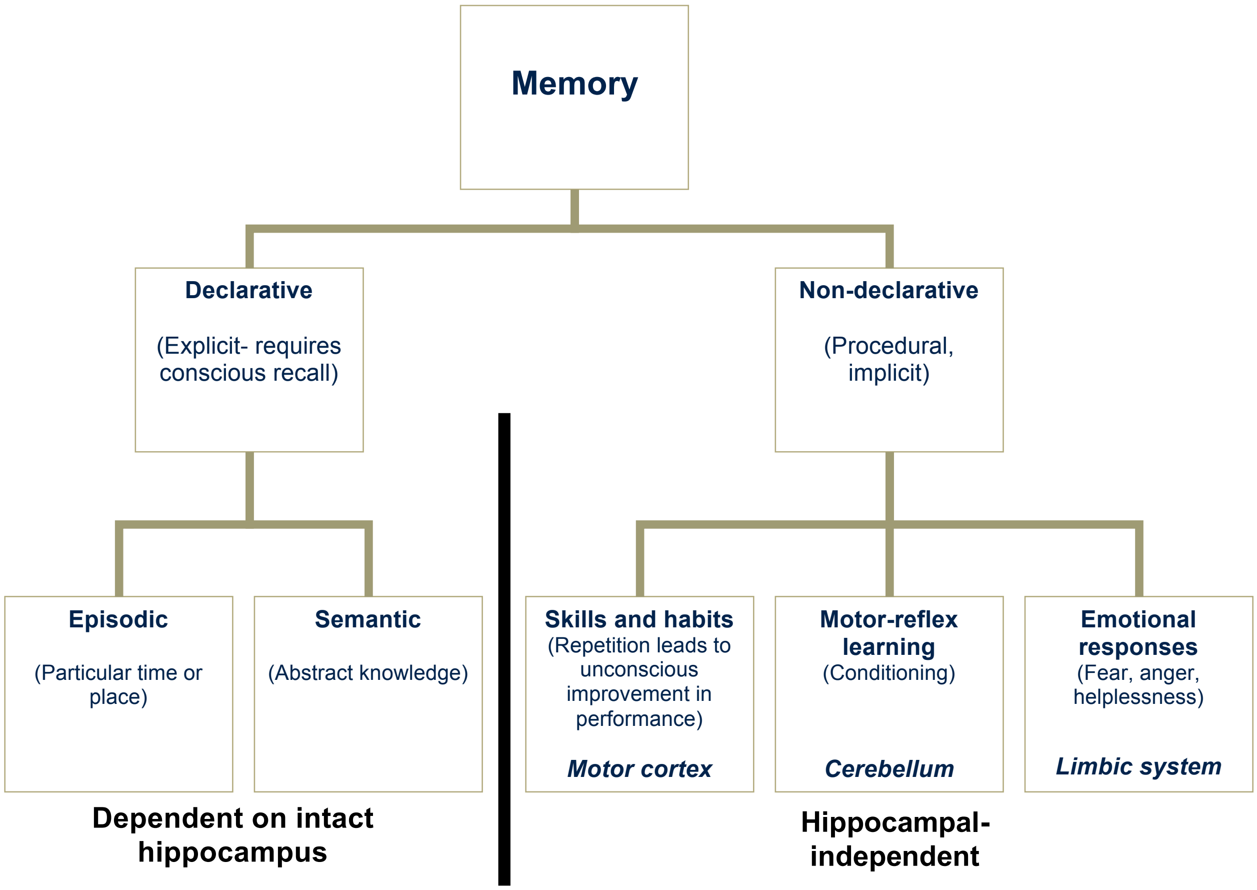

Figure 1. A hierarchical approach to memory.

remember how these memories were formed. Thus, the memories of training events that affected one's skills are forgotten, yet the skills remain.

The cognitive circuitry involved for non-declarative memory does not involve the hippocampus. Production of motor skills, for example, is dependent on the motor cortex. The cerebellum is an important structure for motor-reflex learning and conditioning. The amygdalae, located deep within the medial temporal lobes of the brain, are important for learning to associate "neural" signals with fear or anger). These are all important structures for the production of procedural, or implicit, memories.

Consider the case of a well-trained warfighter on patrol in a hostile, urban environment. An environmental cue, perhaps a sight or sound, prompts the warfighter to raise his weapon to his shoulder, remove the safety, and take aim. This complex skill is accomplished without "thinking about it", implying that the memory for this motor task is *non-declarative*. Assume further that this well-trained warfighter has a target in his sights. Target recognition and assignment may require stored information about civilians and non-U.S. personnel such as local and coalition forces before a weapon is discharged. This type of information comes from *declarative* memory. This hierarchy is shown in Figure 1.

2 ENHANCING MEMORY FUNCTIONS

The cerebellum is an important brain structure for memory formation. It is considered a crucial structure for observed behavior of motor reflex control and learning. However, cerebellar activity is a understudied area with

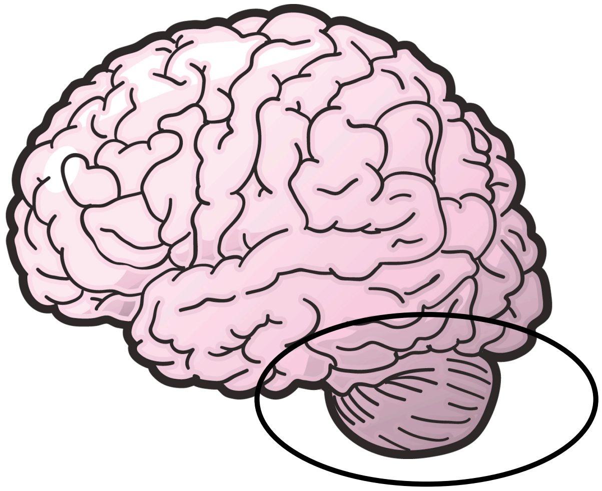

Figure 2 The cerebellum

respect to neural function. Recent advances suggest the cerebellum is involved in higher-level decision-making and planning, and the memory trace circuit has been localized to the cerebellum (Thompson, 2005). Figure 2 shows the relative positions of the cerebellum in the brain.

2.1 Memory storage

Declarative memory is the aspect of memory that consists of experiences and facts that can be recalled. Episodic memories usually result from a single exposure to a specific temporospatial event, while semantic memories contain theoretical knowledge and can be strengthened by repetition. The hippocampus has long been understood as the neural structure that store episodic memories, for those individuals with intact hippocampi. Interesting new research suggests, however, that episodic memories are consolidated in the neocortex and eventually erased from the hippocampus (Deisseroth et al., 2004). Semantic memory is believed to be based in the temporal neocortex, with sensory aspects of knowledge stored in other parts of the cortex.

2.2 Genetic basis

Over 360 genes are unusually active in neurons during learning. The presence or absence of certain of these DNA sequences, or alleles, can lead to increased or decreased memory skills and behavior problems. Alleles of certain genes have also been linked to genetically-based sociopathic behavior and memory difficulties. Other genes may be responsible for traits that lead to poor training response; these may include hearing loss, attention deficit, poor coordination, and so on.

Genetic testing could be used to identify individuals who may have difficulty performing certain tasks or have certain memory aptitudes or deficiencies. For example, 5-hydroxytryptamine2AR (5HT2AR) is the gene responsible for one of 17 of serotonin receptors. A specific recessive allele of this gene has been linked to memory disorders. Further genetics research in this area could prove useful to identify promising occupational specialties that are suited for individuals with different genetic backgrounds. It is easy and inexpensive to test for the presence of alleles such as 5HT2AR using a cheek swab. This may be one technique to select recruits for tasks that best fit their inherent abilities.

2.3 Transcranial Magnetic Stimulation

An emerging technology that may harness the power of the cerebellum is transcranial magnetic stimulation (TMS). TMS reversibly excites or interrupts neural activity by altering magnetic fields in the brain. This alteration has been shown to increase motor reflex learning and reaction time. TMS is accepted as safe and non-invasive, with no long-term effects, and can be used to improve both training and to decrease depression (Davey & Riehl, 2006). The TMS effect can be targeted at specific brain structures, and neuronal activity can be measured with a system combining TMS and EEG technologies (Iramina, Maeno, Kowatari & Ueno, 2002). Repetitive TMS may also yield long-term memory benefits (Naeser, et al., 2005) and even allow individuals to access lower levels of sensory information than they could normally (Snyder, Bahramali, Hawker & Mitchell, 2006). TMS has demonstrated enormous potential, if applied correctly at the applicable times, to enhance training and learning efficacy.

3 SLEEP AND MEMORY

Thirty years of experiments have helped us to understand the relationship between sleep and memory. The type of memory associated with sleep is episodic and semantic. One indication of this relationship is the behaviour of animals trained in a maze using episodic memory that are then prevented from experiencing Rapid Eye Movement (REM) sleep the following night. They have been found to be less likely to do as well in remembering the maze the next day. Comparable results are found in humans. These results help to confirm the existence of a neurophysiological basis for the phenomenon of memory consolidation. While the exact mechanisms are not known, sleep deprivation has been shown to impair the process of storing declarative and procedural memory (Power, 2004). This is especially important in a military training setting, where trainees are balancing a rigorous schedule and often fighting sleep deprivation while also trying to learn new skills and consolidate them for their respective specialties.

3.1 Neurotransmitters

Repetition and rehearsal help consolidate information into memory, and the acetylcholine (ACh) neurotransmitter plays a large role in this process. Two different pathways are found for different memory storage. The ACh travels from the media septum to the hippocampus to store new ideas and produce short-term memories, and also travels from the nucleus basalis to the neocortex, where it may be the switch mechanism for producing long-term memories. During REM sleep, the amount of ACh neurotransmitter is high in the basal forebrain, which promotes neurogenesis and memory formation (Mohapel, Leanza, Kokaia & Lindvall, 2005). Work continues toward finding the consolidation mechanisms. Recent research shows similar EEG and single cell patterns are used for consolidation both during rest and sleep.

The effects of hypocretin peptides, also called orexin peptides, may also be important to sleep and memory. For the last decade, hypocretin has been recognized as a neurotransmitter, but in recent years has research linked it to the waking and sleep cycles (de Lecea et al., 1998). When the levels of these peptides rise, it causes wakefulness, and the decline causes drowsiness and sleep (Lee, Hassani & Jones, 2005). The hypocretin peptides have a positive correlation with EMG activity and fast gamma EEG activity, and have a negative correlation with slow, delta EEG activity. These neuropeptide hormones were originally thought to be primarily oriented to food intake, but are now also linked to sleep regulation and are responsible for narcolepsy.

The blood/brain barrier work at the Defense Sciences Office of the Defense Advanced Research Projects Agency has indicated uses for the application of ACh and hypocretin. For example, it is possible to cause arousal and increase alertness by applying exogenous hypocretin at the correct times. By administering ACh and hypothalamic peptides, it may be possible to induce vigilance during mission-critical conditions and improve memory during drowsy conditions. Other recent findings suggest that periods of slow-wave sleep represent a decoupling of neuronal signaling and consequent background noise reduction. New memories might stand out more easily under these conditions. This research may lead to pharmacological techniques that increase slow-wave sleep and enhance consolidation of new declarative memory.

3.2 Sleep deprivation and memory

Non-human primates have provided a useful test bed for pharmacological agents that are able to enhance or inhibit cognition in human subjects. Monkeys use many of the same neural mechanisms as humans and perform similarly on tasks. In a "delayed matching to sample" test, or DMS test, monkeys were shown a small picture for a few seconds, had a short delay, and then were shown a number of icons and had to move a cursor to the match of the previously shown image. The monkeys showed similar cognitive workload performance to humans: When given a longer delay phase and exposed to more objects in the matching phase, their performance in terms of mean percentage successful matching responses decreased and amount of time to find the appropriate match increased. The effects of both delay and increased sample size were additive. The monkeys also displayed evidence of "category cells", indicative of a hard-wired neural mechanism to recognize familiar objects. For example, some

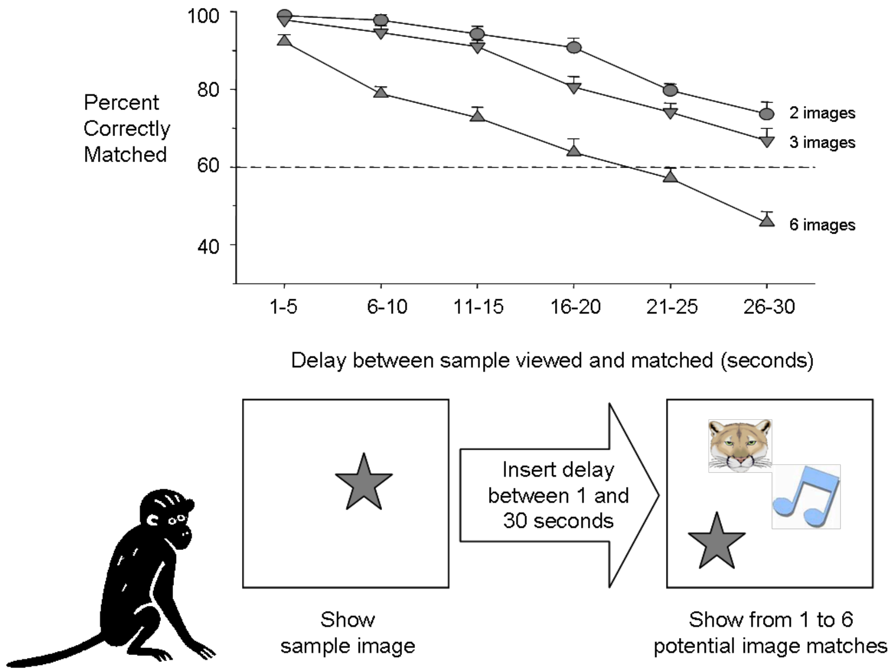

Figure 3 Cognition and performance data in primates

category cells exhibit an increase in neuronal firing when monkeys are shown images of people as opposed to objects, and other cells are better tuned to color pictures rather than the same image in black and white (Hampson, Pons, Stanford & Deadwyler, 2004). Figure 3 provides a graphic of this experiment. The significance of this research on increased workload in humans benefits from the finding that non-human primates and humans share similar cognitive processes.

Extensive research has been done to examine the effects of "smart drugs" on monkeys. The primary drugs in this catagory are ampakines are benzamide compounds that can increase alertness and attention levels. These work by binding to the α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid receptors, also known as AMPA receptors, at the axonal end of a cortical synapse and speeding glutamate adsorption, yielding greater post-synaptic depolarization and faster memory encoding. When monkeys are administered exogenous ampakine, their DMS performance increases and their object recognition mechanisms are enhanced. CX717 is such an ampakine compound, created by Dr. Gary Lynch at UCI in 1993.

The CX717 ampakine formulation has been shown to reverse the adverse cognitive effects of sleep deterioration. T The DMS performance of an individual degrades after 30 to 36 hours without sleep, but can be returned to baseline conditions when ampakine is administered (Porrino, Daunais, Rogers, Hampson & Deadwyler, 2005). The ampakine story is not completely clear, however. A more recent study where subjects were allowed to nap indicated while ampakine can improve recovery after sleep deprivation, CX717 did not enhance cognitive performance relative to treatment with placebo (Cortex, 2006).

Ampakine appears to have no adverse long-term side effects, but the drug may be able to improve memory skills even after leaving the body. A brief treatment with ampakines may result in long lasting increases in Brain-Derived Neurotrophic Factor (BDNF). A strategy could be implemented to administer daily injections of short half-life ampakines to chronically increase BDNF levels. The BDNF would then promote brain plasticity and neuronal viability (Lauteborn et al., 2003).

Sleep deprivation degrades memory by interrupting connections to the prefrontal cortex. Connections from the hippocampus to the prefrontal cortex can interrupt short-term memory and connections from the thalamus to the prefrontal cortex degrade long-term memory. While ampakine CX717 restores the hippocampal-prefrontal cortex link, and a different ampakine, Modafinil, can reconnect the thalamus and prefrontal cortex. Because Modafinal also promotes alertness, the U.S. Air Force currently allows pilots to use Modafinal for some sleep-depriving missions (U.S. Air Force, 2003). Providing warfighters with these pharmacological agents can augment their effectiveness and performance under periods of duress and increase their shift times, thus leading to less manpower needed for a mission.

4 NEW OPPORTUNITIES

Neuroscience is rapidly becoming an important source of ideas for warfighter cognitive and performance enhancement. The advances discussed to this point are under active exploration and have the potential for both short-term and long-term benefits. In addition, many fields are only just beginning to be explored. A few of these are noted here.

- *Imitation learning*. Mirror neurons, which have been observed in primates, are neuron that fire both when an action is performed and when the same action is observed performed by another. Exploiting this discovery could be a tremendous advantage for leading by example or language learning, and it could provide a neural basis for predicting another's actions and inferring intentions.

- *Role of cortical structures.* Because much of the cortex is not hard-wired, the role of many structures, including the cerebellum, thalamus, and basal ganglia, may be different in different individuals, or during different learning processes.

- *Brain asymmetry.* Concepts of local area specificity/functionality are changing; examples include corpus collosum, Broca’s area, and Wernicke’s area. By examining brain asymmetry and its specificity and functionality, researchers can better understand localized and distributed memory and learning processes. New neural imaging technology will aid this investigation.

- *Neuron dynamics.* By understanding how glia produce myelin and create insulated axons, scientists could replicate the process and enhance neuron transmission speed, thereby increasing the speed of learning.

- *Neural prostheses.* Replacement parts that function normally are increasingly being used to treat the wounded or disabled. Substitutes for the cochlea, retina, and central nervous system can be used to restore perceptual abilities. Because medical techniques can save more warfighters today than ever before, more warfighters survive with injuries and debilitations, and these aids can be used to help them restore a normal life. Eventually, replacement parts for the brain may become available.

- *Neuroeconomics*. How humans perform split-second cost-benefit analyses and dynamic decision-making may eventually be measured and understood as neuroimaging technology continues to advance. Techniques may be discovered to train implicit decision making in a socially complex environment.

- *Social neuroscience*. This emerging interdisciplinary field considers the mutual implications of neuroscience and social science toward understanding of social and affective aspects of behavior.

5 CONCLUSIONS

The application of new neuroscience research in military training and operation settings shows great promise to improve warfighter performance. Advances in understanding the processes in the brain and ways to affect those processes can improve troops’ cognitive abilities from the beginning of training to combat situations and even after they leave active duty.

The use of non-invasive neuroimaging technologies and pharmacological agents to improve performance is increasingly warranted by these findings, as well as screening recruits in order to find their aptitudes and specialties that fit their cognitive abilities. As neuroscience rapidly advances, it is increasingly important that the military community keep abreast of discoveries to best aid warfighters.

6 REFERENCES

Cortex News. (2006). Findings on CX717 from the DARPA-sponsored shift work simulation study. Retrieved June 28, 2007, from http://www.cortexpharm.com/html/news/06/06-21-06.html.

Davey, K. R. & Riehl, M. (2006). Suppressing the surface field during transcranial magnetic stimulation. *IEEE Transactions on Biomedical Engineering*, 53 (2), 190-194.

Deisseroth, K., Singla, S., Toda, H., Monje, M., Palmer, T. D., & Malenka, R. C. (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron,* 42 (4), 535-52.

de Lecea, L., Kilduff, T. S., Peyron, C., Gao, X.-B., Foye, P. E., Danielson, P. E., Fukuhara, C., Battenberg, E. L. F., Gautvik, V. T., Bartlett II, F. S., Frankel, W. N., Van den Pol, A. N., Bloom, F. E., Gautvik, K. M. & Sutcliffe, J. G. (1998). The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. *Proceedings of the National Academy of Sciences,* 95 (1), 322-327.

Hampson, R. E., Pons, T. P., Stanford, T. R., & Deadwyler, S. A. (2004). Categorization in the monkey hippocampus: A possible mechanism for encoding information into memory. *Proceedings of the National Academy of Sciences*, 101 (9), 3184-3189.

Iramina, K.; Maeno, T.; Kowatari, Y.; & Ueno, S. (2002). Effects of transcranial magnetic stimulation on EEG activity, *IEEE Transactions on Magnetics*, 38 (5), 3347 - 3349.

Lauterborn, J. C., Truong, G. T., Baudry, M., Bi, X., Lynch, G. & Gall, C. M. (2003). Chronic elevation of brain derived neurotrophic factor by ampakines. *Journal of Pharmacology And Experimental Therapeutics*, 307, 297-305.

Lee, M. G., Hassani, O. K., & Jones, B. E. (2005). Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. *Journal of Neuroscience,* 25 (28), 6716-6720.

Mohapel, P., Leanza, G., Kokaia, M., & Lindvall, O. (2005). Forebrain acetylcholine regulates adult hippocampal neurogenesis and learning. *Neurobiological Aging*, 26 (6), 939-46.

Naeser, M. A., Martin, P. I., Nicholas, M, Baker, E. H., Seekins, H., Helm-Estabrooks, N., Cayer-Meade, C., Kobayashi, M., Theoret, H., Fregni, F., Maria-Tormos, J., Kurland, J., Doron, K. W., & Pascual-Leone, A. (2005). Improved naming after TMS treatments in a chronic, global aphasia patient–Case report. *Neurocase*, 11, 182-193.

Porrino, L. J., Daunais, J. B., Rogers, G. A., Hampson, R. E., & Deadwyler, S. A. (2005). Facilitation of task performance and removal of the effects of sleep deprivation by an ampakine (CX717) in nonhuman primates. *PLoS Biology,* 3 (9), e299.

Power, A. E. (2004). Slow-wave sleep, acetylcholine, and memory consolidation. *Proceedings of the National Academy of Sciences*, 101 (7), 1795-1796.

Snyder, A., Bahramali, H., Hawker, T. & Mitchell, D. J. (2006). Savant-like numerosity skills revealed in normal people by magnetic pulses. *Perception*, 35, 837-845.

Thompson, R. F. (2005). In search of memory traces. *Annual Review of Psychology,* 56, 1-23.

U.S. Air Force Memorandum. (2003). Modafinal and Management of Aircrew Fatigue. Dated 2 December. Retrieved June 28, 2007, from http://www.hep.afrl.af.mil/HEPF/Policy/modafinil.pdf.